Outcomes of biliary atresia in the Nordic countries - a multicenter study of 158 patients during 2005-2016

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Outcomes of biliary atresia in the Nordic countries – a multicenter study of 158 patients during 2005–2016☆,☆☆

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ABSTRACT

Background/purpose: Biliary atresia is the most common reason for newborn cholestasis and pediatric liver transplantation. Even after normalization of serum bilirubin after portoenterostomy, most patients require liver transplantation by adulthood due to expanding fibrosis. We addressed contemporary outcomes of biliary atresia in the Nordic countries.

Methods: Data on center and patients characteristics, diagnostic practices, surgical treatment, adjuvant medical therapy after portoenterostomy, follow-up and outcomes were collected from all the Nordic centers involved with biliary atresia care during 2005–2016.

Results: Of the 154 patients, 148 underwent portoenterostomy mostly by assigned surgical teams at median age of 64 (interquartile range 37–79) days, and 95 patients (64%) normalized their serum bilirubin concentration while living with native liver. Postoperative adjuvant medical therapy, including steroids, ursodeoxycholic acid and antibiotics was given to 137 (93%) patients. Clearance of jaundice associated with young age at surgery and favorable anatomic type of biliary atresia, whereas annual center caseload >3 patients and diagnostic protocol without routine liver biopsy predicted early performance of portoenterostomy. The cumulative 5-year native liver and overall survival estimate was 53% (95% CI 45–62) and 88% (95% CI 83–94), respectively. Portoenterostomy age <65 days and annual center caseload >3 patients were predictive for long-term native liver survival, while normalization of serum bilirubin after portoenterostomy was the major predictor of both native liver and overall 5-year survival.

Conclusions: The outcomes of biliary atresia in the Nordic countries compared well with previous European studies. Further improvement should be pursued by active measures to reduce patient age at portoenterostomy.

Retrospective prognosis study: Level II.

Biliary atresia (BA) is a severe cholangiopathy of infancy and the most common reason for neonatal cholestasis and pediatric liver transplantation (LT) [1,2]. Pathophysiology of BA remains unclear, but rapidly progressing biliary fibrosis leads to liver failure and death within 2 years if untreated [1,2]. The first line surgical treatment is portoenterostomy (PE), which typically resolves cholestasis in around half of the patients [3–6]. Even after normalization of serum bilirubin levels, approximately 70–80% of patients require LT by adulthood due to portally expanding ductal reaction and fibrosis associated with complications of ensuing portal hypertension [1,2,7,8]. Outcome of PE carries vital prognostic

Abbreviations: BA, biliary atresia; LT, liver transplantation; PE, portoenterostomy; ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography; CI, confidence interval; OR, odd ratio; HR, hazard ratio.

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significance in BA, because successful PE circumvents the high waiting list mortality during infancy and increases survival after LT compared to primary LT [9–11].

Several patient-dependent factors at the time of PE such as young age, favorable anatomy of the biliary tract remnant, absence of associated congenital malformations and lower stage of liver fibrosis associate with increased PE success rates and improved native liver survival [1,3,4,6,12]. Different postoperative adjuvant medications have been applied to improve PE outcomes. Although randomized trials have failed to show improvement in native liver survival by steroid treatment after PE [13,14], steroids do seem to increase the proportion of patients who clear their jaundice [15,16], while both steroids and ursodeoxycholic acid have a beneficial effect on liver biochemistry [15–17]. Antibiotic prophylaxis aims to prevent recurrent cholangitis episodes, which may jeopardize survival with native liver [3,18]. Adjuvant therapy regimens combining all three above mentioned medications have improved outcomes in small retrospective studies [19,20]. Concentration of clinical experience with BA management has also been shown to improve outcomes, which has led to centralization of BA in several countries such as UK and Finland [21,22].

In recent large European studies the clearance of jaundice rate and the 5-year native liver survival have ranged between 36–55% and 39–46%, respectively [3–5], whereas no data on collective outcomes in the Nordic countries are available. The Nordic countries has a combined population of 27 million people, share similar healthcare systems, socioeconomic status and educational level, and perform LT within a joint organ exchange organization [11]. The principal aims of this study were to characterize current management practices, analyze recent outcomes of BA and assess factors affecting timing and success rate of PE and native liver survival in the Nordic countries.

1. Patients and methods

1.1. Study design and data collection

This was an international multicenter retrospective observational survey. All children with confirmed BA born in the Nordic countries during 1.1.2005–30.6.2016 and followed-up at least for 4 months were included. Data were collected locally by pediatric surgeons, pediatric hepatologists and pediatricians in all Nordic centers involved with the treatment of BA according to a collectively approved questionnaire and data extraction sheet. The participating centers included one from Denmark (Copenhagen), Finland (Helsinki) and Norway (Oslo), and three from Sweden (Stockholm, Gothenburg, Lund), while no BA patients were reported from Iceland during this time period. All participating centers, excluding Lund, also perform pediatric LT within the Scandiatransplant organ exchange organization [11]. The diagnosis of BA was confirmed based on clinical history, laboratory results, surgical findings, imaging such as perioperative cholangiography, endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), liver biopsy and histopathological assessment of the biliary remnant according to local preferences. Patients, who had undergone PE but proved to have Alagille syndrome ($n = 3$) were excluded.

Clinical practices concerning diagnostic modalities, surgical approach to PE and medical therapy and esophageal variceal surveillance after PE were enquired from each center. Data registered for each patient included gender, ethnicity, timing and type of initial operative management (PE, LT or no operation), anatomic type of BA: extrahepatic bile duct obstruction at the level of the common bile duct (type 1), the hepatic duct (type 2) or the porta hepatis (type 3) according to the Japanese Society of Pediatric Surgeons classification [23], observed associated congenital anomalies, presence of asplenia or polysplenia, use of adjuvant medical therapy after PE including steroids, ursodeoxycholic acid or antibiotic cholangitis prophylaxis, clearance of jaundice, endoscopically detected esophageal varices and listing, performance and timing of LT, and data on death. Withdrawal of active treatment and reason for that was also registered. Latest available serum bilirubin concentrations and blood platelet levels while living with native liver were recorded as surrogates of bile flow and portal hypertension among native liver survivors [24]. Clearance of jaundice was defined as decrease in total serum bilirubin below 20 μmol/l at any time point after PE. Physiological foramen ovale, common anatomic variations of cardiac valves or vesicoureteral reflux were not considered congenital malformations.

1.2. Ethics

The ethical review boards at participating hospitals approved the study.

1.3. Statistical analysis

Continuous data are expressed as medians with interquartile ranges (IQR) and categorical data as frequencies unless otherwise stated. Mann–Whitney *U* test was used to compare continuous variables, and χ^2 test to compare frequencies between groups. Cumulative native liver survival (from birth to end of follow-up, LT or death), survival after LT (from LT to end of follow-up or death) and overall survival (from birth to end of follow-up or death) rates were analyzed using Kaplan Meier curves with 95% confidence intervals (CI) and log-rank test. In multivariate analyses, odd ratios (OR) with their 95% CIs were generated with logistic regression models for predictors of age at PE and clearance of jaundice, and hazard ratios (HR) with their 95% CIs with Cox proportional hazards regression models for predictors of 5-year native liver survival. The proportional hazard hypotheses were confirmed graphically and all variables in univariate analyses were entered to multivariate analyses. The variables for multivariate analyses were chosen based on earlier literature [3–6]. The level of significance was set at $p < 0.05$. Statistics were calculated with StatView® 512 software (Brain Power, Calabasas CA, USA).

2. Results

2.1. Center characteristics

The median number of patients treated in the participating six centers annually ranged from 0.7 to 3.7, while only two centers managed over three patients annually (Supplementary Table 1). Cholescintigraphy, operative cholangiography and ultrasound were uniformly used diagnostic investigations, whereas preoperative diagnostic liver biopsy, MRI, PTC and ERC were less commonly employed. In five centers one surgeon or surgical team operated all BA patients and none used laparoscopic surgical approach for PE. Five centers reported routine steroid use after PE, while ursodeoxycholic acid, antibiotic prophylaxis and supplemental fat-soluble vitamins were regularly prescribed after the surgery in all centers. Two centers followed an endoscopic surveillance protocol for esophageal varices.

2.2. Patient characteristics

In total, 158 patients were identified (Fig. 1). Treatment was withdrawn in four cases (2.5%) due to untreatable severe associated malformations affecting the heart or the central nervous system, and they were excluded from further analyses. Of the remaining 154 patients, 148 underwent PE and six (3.9%) had a primary LT. During the study period, 58 patients had undergone a secondary LT after PE, and 137 (89%) of the actively treated patients were alive. Median follow-up time among all patients was 4.9 (1.8–7.9) years.

The majority of patients were of European origin with a slight female predominance (Table 1). The most unfavorable anatomic type of BA (type 3) was observed in 82% of patients and 27% of patients had any associated congenital malformations, which affected the spleen in 12% and the heart in 6.5%. The vast majority of patients had received

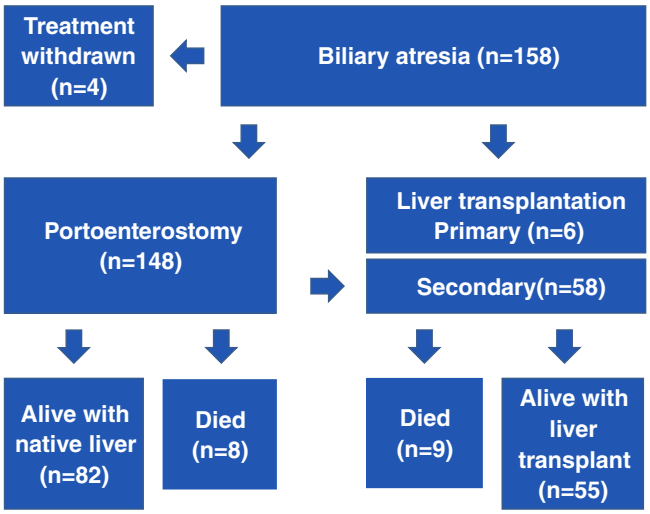

Fig. 1. Biliary atresia patients treated in the Nordic countries.

steroids, ursodeoxycholic acid and antibiotics following PE in order to improve bile flow and prevent cholangitis (Table 1). Of the 148 patients, who underwent PE, 137 (93%) had been treated with all these three adjuvant medications postoperatively.

2.3. Clearance of jaundice

In total, 95 of the 148 patients (64%) normalized their serum bilirubin concentration after PE, while living with their native livers. The patients who cleared their jaundice were median 10 days younger at PE [58 (31–74) days] than those who did not [68 (45–84) days, $p < 0.037$]. In addition to younger age at surgery, favorable anatomy of the biliary tract remnant (BA types 1 and 2) was associated with increased clearance of jaundice rate after PE, and favorable anatomic type of BA remained as the only significant prognosticator in multivariate analysis (Table 2). Gender, ethnicity, associated congenital malformations, splenic malformations or annual center caseload were not significantly associated with clearance of jaundice.

Table 1
Characteristics of actively treated biliary atresia patients during 2005–2016 in the Nordic countries.

Number	154
Females, n (%)	83 (54)
European ethnicity, n (%)	124 (81)
Anatomic type of BA, n (%)	
Type 1	10 (6.4)
Type 2	15 (9.7)
Type 3	126 (82)
Unknown	3 (1.9)
Associated congenital malformations, n (%)	42 (27)
Asplenia or polysplenia	19 (12)
Cardiac defect	10 (6.5)
Underwent portoenterostomy, n (%)	148 (96)
Age at portoenterostomy, days, median (interquartile range)	64 (37–79)
Medical therapy after portoenterostomy, n (%)	
Corticosteroids	137 (93)
Ursodeoxycholic acid	144 (97)
Antibiotics	145 (98)
Normalized serum bilirubin <20 μmol/l, n (%)	95 (64)
Native liver survivors, n (%)	82 (53)
Follow-up age, years, median (interquartile range)	4.9 (2.4–7.3)
Serum bilirubin, μmol/l, median (interquartile range)	6 (4–15)
Blood platelets, 10^9/l, median (interquartile range)	230 (128–303)
Esophageal varices, n (%)	13 (16)

Table 2
Predictors for normalization of serum bilirubin concentration (<20 μmol/l) after portoenterostomy during 2006–2016 in the Nordic countries. Clearance of jaundice rates were compared with χ^2 test and odd ratios for multivariate analysis were generated with logistic regression model.

Predictor	Clearance of jaundice, n (%)	p-value	Odd ratio (95% CI)	p-value
Portoenterostomy age				
<65 days	55/77 (71)	0.056	1.98 (0.92–4.24)	0.079
>65 days	40/71 (56)			
Gender				
Female	50/79 (63)	0.807	0.95 (0.46–1.98)	0.900
Male	45/69 (65)			
European ethnicity				
Yes	76/119 (64)	0.868	0.92 (0.36–2.34)	0.863
No	19/29 (66)			
Anatomic type of BA				
type 1 or 2	20/24 (83)	0.031	3.70 (1.14–12.0)	0.030
type 3	74/123 (60)			
Associated malformations				
Yes	27/41 (66)	0.794	1.09 (0.39–3.03)	0.868
No	68/107 (63)			
Splenic malformations				
Yes	11/18 (61)	0.771	0.70 (0.18–2.81)	0.619
No	84/130 (65)			
Center annual caseload				
>3	54/79 (68)	0.258	1.53 (0.73–3.20)	0.262
<3	41/69 (59)			

2.4. Native liver survival and function

Including the six patients who underwent primary LT, the 5- and 10-year native liver survival estimates were 53% (95% CI 45–62) and 45% (95% CI 35–55), respectively (Fig. 2). The respective native liver survival estimates were 55% (95% CI 47–64) and 47% (95% CI 37–57) following PE. In univariate analysis PE age <65 days, annual center caseload >3 and normalization of serum bilirubin after PE were predictive for long-term native liver survival (Table 3 and Fig. 3). In multivariate analysis, clearance of jaundice and annual center caseload >3 remained highly predictive for the 5-year native liver survival, while the male gender emerged as an additional statistically significant protective factor. Ethnicities, anatomic types of BA or associated congenital malformations, including the splenic ones, were not associated with native liver survival.

Among the 82 patients, who were currently alive with their native livers, median serum bilirubin concentration and blood platelet level was in the normal range (Table 1). Of them, 16% had endoscopically verified esophageal varices, and only two were listed for LT.

2.5. Age at PE

Among the 148 patients, who underwent PE, the surgery was performed at mean age of 60 (range 4–165) days (Table 1). Considering the prognostic importance of the timing of PE for clearance of jaundice and native liver survival, factors associated with the PE age were addressed further. As shown in Table 4, associated congenital malformations, especially the splenic ones, and annual center caseload >3 patients were associated with a greater chance to undergo PE before the age of 65 days, whereas routine use of diagnostic preoperative liver biopsy markedly increased the risk of delayed surgery. The absolute age at PE was median 48 (30–69) days in patients with associated congenital anomalies versus 67 (39–83) days ($p = 0.019$) in those without; 44 (27–58) days in patients with splenic malformations versus 67 (39–80) days ($p = 0.018$) in those without; 52 (29–80) days in centers with >3 annual patients versus 69 (45–79) days ($p = 0.092$) in centers with <3 patients; and 72 (67–82) days in centers routinely using diagnostic preoperative liver biopsy and 52 (28–78) days ($p = 0.0002$) in centers not routinely using preoperative liver biopsy. In multivariate analysis, routine use of preoperative diagnostic liver biopsy

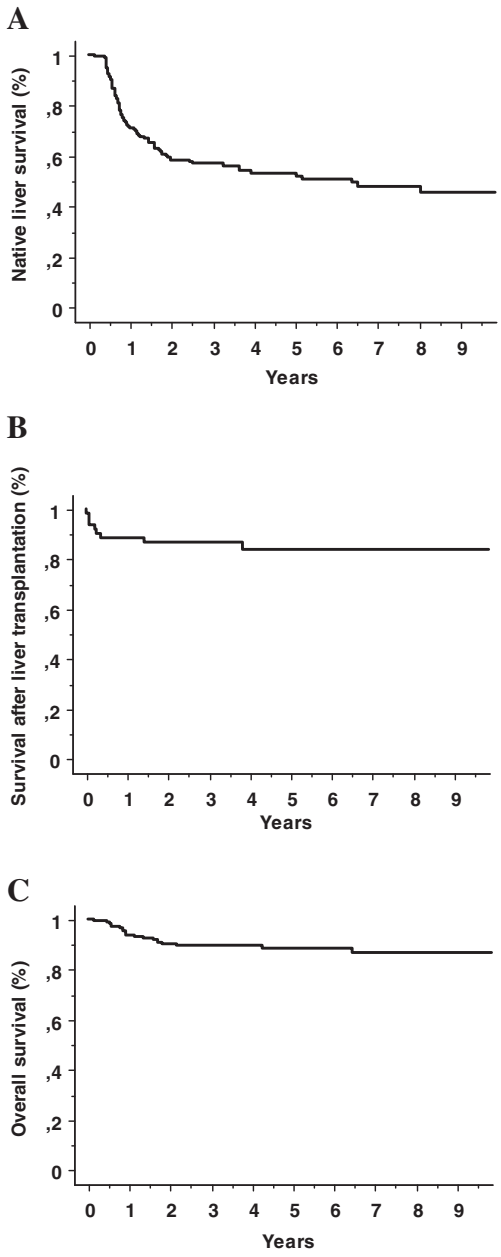

Fig. 2. Survival outcomes of 154 actively treated biliary atresia patients in the Nordic countries. Kaplan Meier survival curves are shown for (A) native liver survival (B) post liver transplantation survival and (C) overall survival.

was the most significant predictor of the PE age, increasing the risk of delayed surgery by 4.3 fold (Table 4).

2.6. Liver transplantation

Six patients with a delayed diagnosis were transplanted primarily without a prior PE at median age of 193 (154–281) days. In total, eight patients (5.1%) died without receiving a liver graft and nine patients died after LT (Fig. 1). Overall median age at LT was 0.82 (IQR 0.58–1.76, range 0.40–10.1) years. Including all 64 transplanted patients, both the 5- and 10-year survival estimates after LT were 84% (95% CI 74–94) (Fig. 2). The respective figures were 85% (95% CI 75–95) among the patients, who had undergone a prior PE before transplanted. Ethnicities, gender, anatomic types of BA, clearance of jaundice, associated congenital anomalies or splenic malformations were not associated with the 5-year survival after LT (data not shown).

Table 3
Predictors for native liver survival after portoenterostomy during 2006–2016 in the Nordic countries. Five-year native liver Kaplan Meier survival rates were compared with log-rank test and hazard ratios for multivariate analysis were generated with Cox regression model.

Predictor	n	5-year survival (%) (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Portoenterostomy age					
<65 days	77	66 (55–78)	0.005	1.51 (0.80–2.87)	0.207
>65 days	71	44 (32–56)			
Gender					
Female	79	51 (39–63)	0.301	0.47 (0.26–0.85)	0.012
Male	69	60 (48–72)			
European ethnicity					
Yes	119	54 (45–64)	0.692	0.70 (0.35–1.41)	0.318
No	29	60 (42–79)			
Anatomic type of BA					
type 1 or 2	24	66 (44–87)	0.187	1.36 (0.58–3.18)	0.485
type 3	123	53 (43–62)			
Associated malformations					
Yes	41	62 (46–78)	0.612	1.02 (0.43–2.45)	0.966
No	107	53 (43–63)			
Splenic malformations					
Yes	18	49 (24–74)	0.546	0.75 (0.25–2.24)	0.601
No	130	56 (47–65)			
Center annual caseload					
>3	79	66 (54–77)	0.004	3.46 (1.76–6.81)	0.0003
<3	69	44 (32–56)			
Clearance of jaundice					
<20 μmol/l	95	86 (78–94)	<0.0001	32.0 (14.8–69.2)	<0.0001
≥20 μmol/l	53	4.3 (0–10)			

2.7. Overall survival

The 5- and 10-year overall survival estimates were 88% (95% CI 83–94) and 87% (95% CI 81–93), respectively (Fig. 1). The 5-year overall survival was higher among patients who cleared their jaundice after PE [98% (95% CI 95–100)] than among those who did not [73% (95% CI 61–86)], $p < 0.0001$, and tended to be lower among the patients with splenic malformations [77% (95% CI 57–97)] than in patients without [90% (95% CI 84–95)], $p = 0.064$. In univariate analysis ethnicities, gender, anatomic types of BA, annual center caseload or associated congenital anomalies were not associated with the 5-year overall survival (data not shown).

3. Discussion

The results of this study show that the clearance of jaundice rate, the 5-year native liver survival after PE and overall survival in the Nordic countries compared well with previous European studies (Table 5). Following PE, serum bilirubin concentration normalized in 64%, and 55% of the Nordic patients were alive with their native livers at 5 years. Their median serum bilirubin and blood platelet levels were in the normal range, reflecting well-preserved native liver function. The diagnostic and management practices of BA were relatively uniform in the Nordic countries, and the great majority of the patients received a combination adjuvant therapy after PE, including steroids, ursodeoxycholic acid and antibiotics.

Although only around 20–30% of the BA patients reach adulthood without undergoing LT [7,25], extended native liver survival following successful PE has the potential to improve overall prognosis of BA in several ways. Firstly, it eliminates the increased waiting list mortality during infancy after failed PE [9,11], which was reflected in the present study by the 98% 5-year overall survival among the patients who cleared their jaundice. Secondly, successful PE and subsequently prolonged

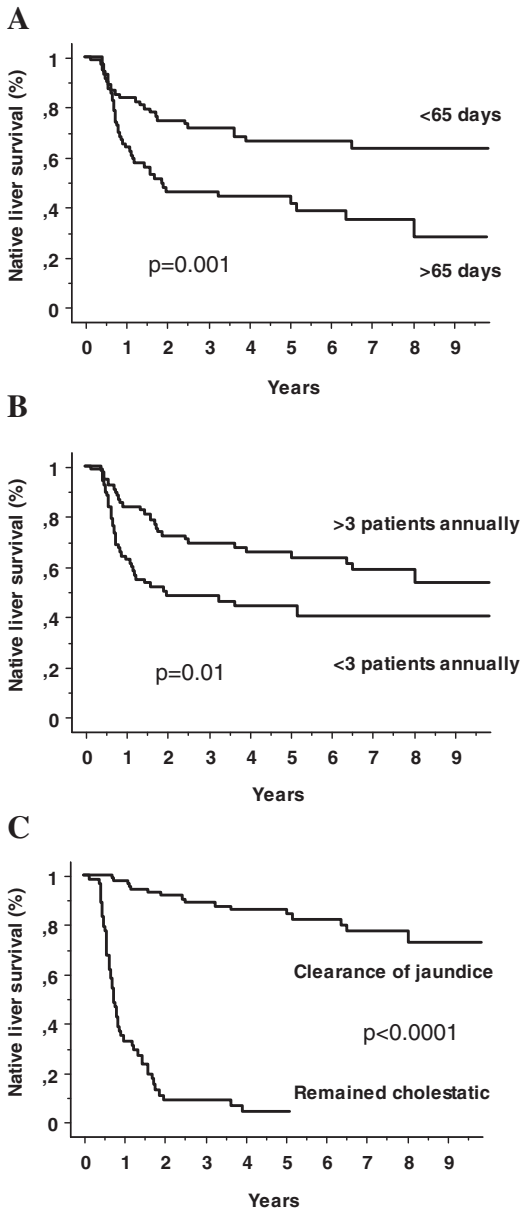

Fig. 3. Native liver survival after portoenterostomy. Kaplan Meier survival curves and log-rank p-values are shown according to (A) age at portoenterostomy (B) annual center caseload and (C) clearance of jaundice.

survival with the native liver seem to improve both the graft and patient survival rates after LT performed later in life [10]. Thirdly, extended survival with native liver shortens the cumulative life-time exposure to toxic side-effects of immunosuppressive medication by postponing the need for LT.

Similarly to previous studies [3,4,26], our findings suggest that patient age at surgery is the major prognostic factor for the success of PE. In the present study, younger age at PE associated with both more frequent clearance of jaundice and better long-term native liver survival. As expected, clearance of jaundice, in turn, was clearly the most important predictor of long-term native liver survival. In the present study, the median patient age at PE (64 days) was 5 to 10 days higher than in other recent European reports from France, the Netherlands and England and Wales (Table 5), offering a logical and realistic target for further improvement of the outcomes. While no screening programs for BA have been yet established in the Nordic countries, all newborns visit a primary care physician at the age of 4–6 weeks. Identification of cholestatic infants at this point at the latest should leave enough time

Table 4
Predictors of portoenterostomy age < 65 days in patients with biliary atresia during 2006–2016 in the Nordic countries. Clearance of jaundice rates were compared with χ^2 test and odd ratios for multivariate analysis were generated with logistic regression model.

Predictor	Portoenterostomy age < 65 days, n (%)	p-value	Odd ratio (95% CI)	p-value
European ethnicity				
Yes	65/119 (55)	0.210	1.17 (0.48–2.87)	0.730
No	12/29 (41)			
Anatomic type of BA				
Type 1 or 2	12/24 (50)	0.799	0.64 (0.24–1.73)	0.376
Type 3	65/123 (53)			
Associated malformations				
Yes	29/41 (71)	0.005	1.46 (0.53–3.74)	0.495
No	48/107 (45)			
Splenic malformations				
Yes	16/18 (89)	0.0008	5.82 (0.99–34.2)	0.051
No	61/130 (47)			
Center annual caseload				
>3	51/79 (65)	0.0011	1.51 (0.64–3.59)	0.350
<3	26/69 (38)			
Liver biopsy based diagnosis				
Yes	7/34 (21)	<0.0001	0.23 (0.08–0.70)	0.010
No	70/114 (61)			

for completion of a well-organized diagnostic protocol and timely performance of PE before the age of 2 months. General awareness of newborn cholestasis and the practice of routine measurement of serum conjugated bilirubin in all jaundiced newborns older than 2 weeks could be endorsed by active education [27–29]. Stool color card screening has improved timing of PE, clearance of jaundice and native liver survival in Taiwan and Japan, where BA incidence is considerably higher than in Europe [30,31].

Despite early recognition of cholestatic newborns, the in-hospital delay related to diagnostic protocols or logistic problems may also unnecessarily delay the primary surgical care. We found that routine use of preoperative diagnostic liver biopsy associated with delayed performance of PE, whereas annual caseload >3 patients associated with timely surgery. However, our survey did not look for differences in the age at first referral to tertiary centers. Theoretically, the two centers practicing routine liver biopsies may have received their referrals at a later age than the others. Furthermore, the recently published joint European and North American guidelines do in fact recommend the use of liver biopsy for evaluation, in particular because of its high specificity for BA [12,29]. Taken together, our findings imply, that any chosen diagnostic pathway should be critically evaluated and optimized to circumvent all avoidable delays, while increasing number of patients may help to put final touches in these processes.

Besides age at PE, annual center caseload >3 patients associated with improved native liver survival in the present survey. Centralization of BA treatment and increasing caseloads has been shown to improve native liver and overall survival in England and Wales as well as in Finland and Denmark [21,22,32]. In contrast, no differences in outcomes were observed between hospitals with the lowest and highest caseloads in France and Canada ranging from below two to over 20 patients per year [33,34]. BA treatment results are collectively influenced by the quality of each step of the care, including early diagnosis, appropriate surgery, postoperative management and follow-up. Because caseload was not associated with normalization of serum bilirubin after PE, other steps of the care pathway than surgical management are possibly more sensitively affected by the caseload. In order to maximize surgical

Table 5
Recently reported outcomes of biliary atresia in Europe.

Origin (reference)	Period	Cohort size	Median age at PE (days)	Clearance of jaundice (%)	5-year native liver survival (%)	5-year overall survival (%)
England and Wales [5]	1999–2009	439	54	55	46 (95% CI 41–51)*	90 (95% CI 88–93)
France [4]	2003–2009	339	59	36	39 (SE 3.3%)†	89 (SE 1.9%)
Netherlands [3]	1998–2008	104	59	38	42 (95% CI 32–52)†‡	76 (95% CI 68–85)‡
Nordic countries (present)	2005–2016	154	64	64	53 (95% CI 45–62)*	88 (83–94)

PE, portoenterostomy.
LT, liver transplantation.
* Includes all patients.
† Includes patients who underwent PE.
‡ Four-year survival.

experience, the relatively low caseload in each country was compensated by concentrating PE operations to one surgeon in most Nordic centers.

In this study the presence of associated congenital anomalies, including the splenic malformations, was not associated with decreased clearance of jaundice or native liver survival rates in contrast to some previous studies [4]. This could be explained by the observation that these patients underwent PE at younger age than others possibly following an earlier BA diagnosis inflicted by discovery and investigation of their associated congenital anomalies. The prevalence of splenic malformations and congenital cardiac defects was comparable to previously reported figs. [35,36], while occurrence of any associated malformation was somewhat higher than in previous studies [35–37].

There is evidence on postoperative steroids improving clearance of jaundice rate and liver biochemistry following PE [15,16], although randomized trials have failed to demonstrate benefit of postoperative steroids on native liver survival [13,14]. Ursodeoxycholic acid has a favorable effect on serum liver biochemistry [17], while antibiotic prophylaxis may reduce recurrent cholangitis episodes and improve native liver survival after successful PE [3,18]. Interestingly, two retrospective studies have reported improvements in clearance of jaundice and native liver survival rates after PE with postoperative adjuvant therapy consisting of steroids, ursodeoxycholic acid and antibiotics [19,20]. Although our study was not design to address the effectiveness this triple adjuvant therapy, it could be one factor contributing to the achieved outcomes. Obviously, a randomized controlled trial would be the optimal way to address this question further.

This study had several limitations. Because only two centers followed an endoscopic surveillance protocol, the incidence of varices is most likely markedly underestimated. We did not collect data on cholangitis episodes, serum bilirubin concentrations at set time points or the time taken to achieve clearance of jaundice and thus were not able address their effects on survival outcomes. Nor did we collect details or duration of postoperative medical therapy following PE. However, availability and accuracy of such data always remains imperfect in a retrospective study design and our major aim was to assess management characteristics and outcomes of BA in the Nordic countries.

In conclusion, these findings demonstrate that current outcomes of BA in the Nordic countries are well comparable to previous European studies and annual caseload is highly predictive for the 5-year native liver survival. Further improvement should be pursued by multimodal active measures to reduce patient age at PE. The high rates of clearance of jaundice and native liver survival after PE were achieved with the use of steroids, ursodeoxycholic acid and antibiotics as a postoperative adjuvant medical therapy in over 93% of patients.

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